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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Alberto L. Mendoza

Serial No.: 09/082,112 Group Art Unit: 1647

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For : METHOD AND VACCINE FOR TREATMENT OF PYTHIOSIS INSIDIOSI IN HUMANS AND LOWER ANIMALS

Examiner : Sharon L. Turner

Assistant Commissioner For Patents

Washington, D.C. 20231

REPLY BRIEF UNDER 37 C.F.R. § 1.193

Dear Sir:

In response to the Examiner's Answer, the Applicant remarks as follows.

With respect to the 35 U.S.C. § 112, second paragraph, rejection, the Examiner on page 8 of the Examiner's Answer argues that the term "mixed intracellular proteins" is vague because the soluble material released from the disrupted cells is not a mixture of only intracellular proteins but rather a mixture of both intracellular proteins and extracellular proteins. The extracellular proteins are presumed to be those proteins which have been synthesized by the cell but which have not yet been extruded from the cell.

The terms "extracellular" and "intracellular" are operational terms of art. The term "intracellular

proteins" in the present application refers to proteins destined to remain inside the cell during the life of the cell and the term "intracellular protein preparation" refers to a preparation of proteins isolated from a disrupted cell after the media surrounding the cell has been removed. Any newly synthesized protein in an intracellular protein preparation that is destined to become an extracellular protein is, in most cases, present in a negligible amount and, in most cases, is not properly processed to be an extracellular protein. It is more accurate to refer to such proteins as precursors to extracellular proteins and not extracellular proteins.

The term "extracellular proteins" in the present application refers to proteins which are excreted by the cell into the extracellular environment thus, the term "extracellular protein preparation" refers to a preparation of proteins that have been isolated from the media surrounding a cell. In general, extracellular proteins are distinguishable from their intracellular precursors because of the processing (e.g., cleavage, phosphorylation, glycosylation) such proteins undergo before being excreted into the extracellular environment.

One with ordinary skill in the art is fully aware of the above operational meaning of the terms "intracellular" and "extracellular" with respect to

proteins produced by a cell. When one of ordinary skill in the art is told that a protein preparation consists of extracellular proteins, the ordinary artisan understands that preparation consists essentially of those proteins excreted from a cell or which are possibly attached to the outer surface of the cell (but which are removed when the cells or cell debris are removed). When the ordinary artisan is told that a preparation consists of intracellular proteins, the ordinary artisan understands that the preparation consists essentially of those proteins that are ordinarily found only inside the cell. One skilled in the art is also aware that when cells are disrupted by sonication or the like, a mixture consisting of soluble "intracellular" proteins released from the cell and insoluble "intracellular" proteins and proteins attached to the outer surface of the cell membrane is produced. The insoluble proteins are removed by centrifugation, filtration, or the like to produce the claimed mixture of "intracellular proteins."

Therefore, in the present application, the intracellular protein preparation consists essentially of proteins that are found only in the cell. Any contribution to the intracellular protein preparation by any newly synthesized precursor protein destined to be extracellular would be expected to be negligible.

With respect to "extracellular proteins", in the present application, the extracellular protein preparation consists essentially of proteins that have been excreted from the cell. The fact that the extracellular proteins had been made in the cell is irrelevant because the extracellular protein preparation excludes all proteins that are within the cell or attached to the outer membrane surface.

In light of the above, it is believed that the terms "intracellular proteins" and "extracellular proteins" are clearly and fairly defined such that one of ordinary skill in the art would know what the proteins are present in the intracellular and extracellular fractions comprising the claimed vaccine.

With respect to the 35 U.S.C. § 103(a) rejection, the Examiner asserts on page 12 of the Examiner's Answer that in view of the prior art (in particular, Mendoza (1995) and Mendoza (1996)), which disclose a vaccine containing the 28K, 30K, and 32K cytoplasmic proteins added to the "original *Pythium*-vaccine" (SCAV) (Mendoza (1996): page 159, column 2, lines 15-18) or "culture filtrated proteins" (Mendoza (1995): abstract), it would have been *prima facie* obvious for one skilled in the art to simply mix all the intracellular proteins prepared as disclosed in Mendoza (1992a) or Mendoza (1992b) with the extracellular proteins of the SCAV (Mendoza (1992a)) as it would be

convenient to do so.

The Applicant disagrees because one skilled in the art could not predict the results from the claimed composition which includes all of the soluble intracellular proteins combined with the extracellular proteins of the SCAV compared to the vaccine disclosed by Mendoza (1996) or Mendoza (1995) which contains the extracellular proteins of the SCAV mixed with three immunodominant proteins.

Mendoza (1996) is a review article and Mendoza (1995) is a brief abstract to a scientific meeting. Neither is enabling for *Pythiosis* vaccines because neither disclose methods for preparing intracellular proteins or extracellular proteins. Neither reference is enabling because neither teaches how to obtain the three immunodominant proteins or how to prepare a cell extract which contains the three immunodominant proteins. At best, one skilled in the art must view Mendoza (1996) and Mendoza (1995) in view of a reference which teaches preparing a cell extract which contains the three immunodominant proteins.

Mendoza (1992a) discloses a method for preparing extracellular proteins (SCAV) and a method for preparing intracellular proteins (CMV). However, Mendoza (1992a) does not disclose a method for preparing intracellular proteins in the manner taught by the Applicant. The CMV disclosed in Mendoza (1992a)

includes a mixture of both intracellular proteins and insoluble cell debris which is clearly different than the mixture of intracellular proteins taught by the Applicant which contains only soluble intracellular proteins. Mendoza (1992a) teaches that the CMV produces a prominent inflammatory response when inoculated into a horse, has a short shelf life, and like the SCAV, does not cure chronically infected horses. In light of the undesirable characteristics of the CMV, Mendoza (1992a) states that the SCAV is the vaccine of choice.

While Mendoza (1992a) does not mention that the CMV contains any immunodominant proteins much less the three immunodominant proteins, Mendoza (1992b) identifies the three immunodominant proteins and provides a method based on gel electrophoresis for isolating the three immunodominant proteins. Thus, when viewed together, the prior art provides one of ordinary skill in the art a means for preparing a vaccine which contains extracellular proteins prepared as taught in Mendoza (1992a) and the isolated three immunodominant proteins prepared as taught in Mendoza (1992b) and which would be expected to be useful for curing chronically infected horses as suggested by Mendoza (1995) and Mendoza (1996). However, the prior art does not suggest the Applicant's claimed method using a vaccine containing the mixed intracellular proteins and the mixed extracellular proteins.

In hindsight it might be argued that it would have been *prima facie* obvious to substitute the Applicant's mixed intracellular proteins for the isolated three immunodominant proteins because it would save the time and expense of isolating the three immunodominant proteins. However, at the time of the Applicant's invention one of ordinary skill in the art would not have had the benefit of the Applicant's disclosure. Instead, one of ordinary skill in the art would have had to rely upon the prior art which includes Mendoza (1992a) which teaches that a mixture of intracellular proteins (CMV) does not produce a desirable vaccine. Thus, while one of ordinary skill in the art would know that intracellular protein preparations contain the three immunodominant proteins and that isolating the three immunodominant proteins from the intracellular protein preparations and adding the proteins to a preparation of extracellular proteins produces a desirable vaccine, the skilled artisan would also know that in light of Mendoza (1992a), intracellular protein preparations also appear to contain unidentified components which are undesirable for inclusion in a vaccine. None of the prior art teaches or suggests what these undesirable components are or how to remove them. Thus, it would not have been *prima facie* obvious to one of ordinary skill in the art to make a vaccine comprising a mixture of intracellular

and extracellular proteins and it would not have been *prima facie* obvious to make the vaccine in the manner taught by the Applicant.

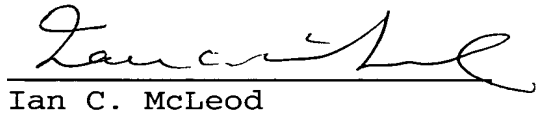
While the Applicant's method for preparing the vaccine is simple that of itself does not preclude patentability. The important steps in the preparation of the Applicant's vaccine appear to include the steps of removing the insoluble cell debris from the soluble intracellular proteins, mixing the soluble intracellular proteins with the extracellular proteins, precipitating the mixture of proteins in acetone, and dialyzing in water produces a desirable vaccine. These steps and the order they are performed produces a vaccine which is not equivalent to a mixture of either the CMV and the SCAV or the intracellular protein preparation in Mendoza (1992b) and the SCAV. Therefore, these steps and the vaccine produced would not have been *prima facie* obvious in view of the prior art.

Even if the Applicant's method for treating animals was *prima facie* obvious, the Applicant's method for treating humans would still not be *prima facie* obvious because of apparent differences in pathogenesis between animals and humans. Pythiosis is a subcutaneous, bone, and lung disease of horses, cats, and cattle; a subcutaneous or intestinal disease of dogs; and a cutaneous, subcutaneous, and blood vessel disease of humans (Mendoza (1992b): page 2980).

Pythiosis produces kunkers in horses but not humans (Mendoza (1996): sentence bridging pages 156-157). The differences between Pythiosis infections in horses verses humans suggest that a vaccine which was effective for curing horses might not be efficacious in humans infected with Pythiosis. Thus, the Applicant's claimed method for treating humans would not have been *prima facie* obvious.

In light of the above and the Applicant's Appeal Brief, the Applicant's claimed method is patentable. Reversal of the final rejection and remand to the Examiner for allowance is requested.

Respectfully,



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